

WHAT IS CLAIMED IS:

1. A method for treating a patient having a condition mediated by neurotoxicity, neurodegeneration or neurological damage, comprising administering to said patient a therapeutically effective amount of a peptide comprising one or more monomeric peptides of 8 to about 40 amino acids in length that bind to EPO receptor, each monomeric peptide comprising a sequence of amino acids $X_4X_5X_aX_bX_cX_dX_7$ (SEQ ID NO: 47), wherein

X_a is G or A;

X_b is P or A;

X_c is T or A;

X_d is selected from W, A, and F;

X_4 is selected from R, H, Y, L, and W, or X_4 is nonexistent;

X_5 is selected from F, M, and I;

X_6 is independently selected from the 20 genetically coded L-amino acids or the stereoisomeric D-amino acids; and

X_7 is selected from D, V, E, I, and L.

2. The method of claim 1, wherein said sequence is $X_4X_5GPX_6TWX_7$ (SEQ ID NO: 48).

3. The method of claim 2, wherein said sequence is $X_3X_4X_5GPX_6TWX_7X_8$ (SEQ ID NO: 1), wherein

X_3 is selected from C, E, A, α -amino- γ -bromobutyric acid, and homocysteine (Hoc); and,

X_8 is selected from C, K, A, α -amino- γ -bromobutyric acid, and homocysteine (Hoc).

4. The method of claim 3 with the proviso that either X_3 or X_8 is C or homocysteine (Hoc).

5. The method of claim 4 wherein X_3 or X_8 is C.

5 6. The method of claim 3 wherein

X_3 is selected from C, E, and A;

X_4 is selected from R, H, and Y, or X_4 is nonexistent;

X_6 is selected from V, L, I, M, E, and A; and

X_7 is D or V; and

X_8 is selected from C, K and A.

7. The method of claim 3 wherein said peptide is a dimer of each of said monomeric peptides comprising a sequence of amino acids $YX_2X_3X_4X_5GPX_6TWX_7X_8$ (SEQ ID NO: 2), wherein

X_2 and X_6 are each independently selected from the 20 genetically coded L-amino acids;

X_3 is C; and

X_8 is C.

8. The method of claim 7 wherein

X_2 is selected from L S H M A and I, or X_2 is nonexistent; and

X_6 is selected from V, L, I, M, E, and A.

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9. The method of claim 7 wherein each of said monomeric peptides comprises a sequence of amino acids $X_1YX_2X_3X_4X_5GPX_6TWX_7X_8X_9X_{10}X_{11}$ (SEQ ID NO: 3), wherein each of X_1 , X_2 , X_6 , X_9 , X_{10} , and X_{11} is independently selected from the 20 genetically coded L-amino acids.

10. The peptide dimer of claim 9 wherein

X_3 is selected from C, E, and A;

X_4 is selected from R, H, and Y, or X_4 is nonexistent;

X_7 is D or V;

X_8 is C or K.

X_9 is K, G, L, Q, R, S, or T; and

X_{10} is A, G, P, R, or Y.

11. The method of Claim 10 wherein

X_1 is D, E, L, N, S, T or V;

X_2 is selected from L, S, H, M, A, and I, or X_2 is nonexistent;

X_9 is selected from K, Q, R, S, and G; and

X_{10} is selected from P, Y, and A.

12. The method of claim 3 wherein said peptide is a dimer of each of said monomeric peptides comprising a sequence of amino acids $X'X_2X_3X_4X_5GPX_6TWX_7X_8$ (SEQ ID NO: 49), wherein X' is selected from D-Tyr, *p*-NO₂-Phe, *p*-NH₂-Phe, *p*-F-Phe, *p*-I-Phe, and 3,5-dibromo-Tyr.

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13. The method of claim 12 wherein said sequence is X'CHFGPLTWVC.

14. The method of claim 1 wherein each of said monomeric peptides comprise a sequence independently selected from

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GGLYLCRFGPVTWDCGYKGG	(SEQ ID NO:7);
GGTYSCHFGPLTWVCKPQGG	(aka EMP-1) (SEQ ID NO:8);
GGDYHCRMGPPLTWVCKPLGG	(SEQ ID NO:9);
VGNYMCHFGPITWVCRPGGG	(SEQ ID NO:10);
GGVYACRMGPITWVCSPLGG	(SEQ ID NO:11);
VGNYMAHMGPIWVCRPGG	(SEQ ID NO:12);
GGTYSCHFGPLTWVCKPQ	(aka EMP-16) (SEQ ID NO:13);
GGLYACHMGPMTWVCQPLRG	(aka EMP-36) (SEQ ID NO:14);
TIAQYICYMGPETWECRPSKA	(aka EMP-38) (SEQ ID NO:15);
YSCHFGPLTWVCK	(aka EMP-20) (SEQ ID NO:16);
YCHFGPLTWVC	(aka EMP-23) (SEQ ID NO:17);
SCHFGPLTWVCK	(aka EMP-24) (SEQ ID NO:18);
GGTASCHFGPLTWVCKPQGG	(aka EMP-6) (SEQ ID NO:19);
GGTYSCHFAPLTWVCKPQGG	(aka EMP-9) (SEQ ID NO:20);
GGTYSCFGPLTWVCKPQGG	(aka EMP-27) (SEQ ID NO:21);
TYSCHFGPLTWVCKPQGG	(aka EMP-17) (SEQ ID NO:22);
TYSCHFGPLTWVCKPQ	(aka EMP-18) (SEQ ID NO:23);
YSCHFGPLTWVCKP	(aka EMP-19) (SEQ ID NO:24);
YSCHFGPLTWVC	(aka EMP-21) (SEQ ID NO:25);
YSCHFGALTWVCK	(aka EMP-22) (SEQ ID NO:26);

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	GGCRIGPITWVCGG	(aka EMP-25) (SEQ ID NO:27);
	HFGPLTWV	(aka EMP-26) (SEQ ID NO:28);
	GGTTSCHFGPLTWVCKPQGG	(aka EMP-7) (SEQ ID NO:29);
	GGTFSCHFGPLTWVCKPQGG	(aka EMP-8) (SEQ ID NO:30);
5	GGTYSCHFGALTWVCKPQGG	(aka EMP-10) (SEQ ID NO:31);
	GGTYSCHFGPATWVCKPQGG	(aka EMP-11) (SEQ ID NO:32);
	GGTYSCHFGPLAWVCKPQGG	(aka EMP-12) (SEQ ID NO:33);
	GGTYSCHFGPLTAVCKPQGG	(aka EMP-13) (SEQ ID NO:34);
	GGTYSCHFGPLTFVCKPQGG	(aka EMP-14) (SEQ ID NO:35);
10	GGTYSCHFGPLTWVCKAQGG	(aka EMP-15) (SEQ ID NO:36);
	GGTXSCHFGPLTWVCKPQGG	(aka EMP-28, X = D-Tyr) (SEQ ID NO:37);
	GGTXSCHFGPLTWVCKPQGG	(aka EMP-29, X = <i>p</i> -NO ₂ -Phe) (SEQ ID NO:38);
	GGTXSCHFGPLTWVCKPQGG	(aka EMP-30, X = <i>p</i> -NH ₂ -Phe) (SEQ ID NO:39);
	GGTXSCHFGPLTWVCKPQGG	(aka EMP-31, X = <i>p</i> -F-Phe) (SEQ ID NO:40);
15	GGTXSCHFGPLTWVCKPQGG	(aka EMP-32, X = <i>p</i> -I-Phe) (SEQ ID NO:41);
	GGTXSCHFGPLTWVCKPQGG	(aka EMP-33, X = 3,5-dibromo-Tyr) (SEQ ID NO:42);
	Ac-GGTYSCHFGPLTWVCKPQGG	(aka EMP-34) (SEQ ID NO:43);
	GGLYACHMGPMTWVCQPLGG	(aka EMP-35) (SEQ ID NO:44);
20	LGRKYSCHFGPLTWVCQPAKKD	(aka EMP-37) (SEQ ID NO:45); and
	GGTYSEHFGPLTWVKKPQGG	(aka EMP-39) (SEQ ID NO:46).

15. The method of claim 14 wherein each of said monomeric peptides is independently selected from:

25	GGTYSCHFGPLTWVCKPQGG	(aka EMP-1) (SEQ ID NO:8);
	GGTASCHFGPLTWVCKPQGG	(aka EMP-6) (SEQ ID NO:19);
	GGTYSCHFAPLTWVCKPQGG	(aka EMP-9) (SEQ ID NO:20); and
	YCHFGPLTWVC	(aka EMP-23) (SEQ ID NO:17).

16. The method of claim 1 wherein said peptide is a dimer formed by a polyethylene glycol linker through a covalent bond.
17. The method of claim 16 wherein each monomeric peptides of said dimer are covalently bound N-terminus to N-terminus.
18. The method of claim 16 wherein each monomeric peptides of said dimer are covalently bound N-terminus to C-terminus.
19. The method of claim 1 wherein said monomeric peptides are dimerized on activated benodiazepins, oxazolones, azalactones, aminimides or diketopiperazine.
20. The method of claim 19 wherein said monomeric peptides are covalently bound N-terminus to N-terminus.
21. The method of claim 19 wherein said monomeric peptides are covalently bound N-terminus to C-terminus.
22. The peptide of claim 2, which comprises least one peptide dimer.
23. A method of activating a cell surface receptor to induce neuroprotective biological activity comprising contacting a dimer of peptides of claim 2 with said receptor thereby inducing said neuroprotective biological activity.
24. The method of claim 23 wherein said cell surface receptor is contacted with said dimer in vitro or in vivo.
25. The method of claim 23 wherein said cell surface receptor is EPO receptor.

26. The method of claim 23 wherein said peptide dimer is a cell surface receptor agonist selected from a group consisting of a GH agonist, PDGF agonist, EGF agonist, G-CSF agonist, TPO (thrombopoietin) agonist, VEGF agonist, FGF agonist, insulin agonist, IL-3 agonist, IL-5 agonist, IL-6 agonist and IL-2 agonist.

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27. The method of claim 23 wherein said agonist comprises a sequence of amino acids $YX_2X_3X_4X_5GPX_6TWX_7X_8$ (SEQ ID NO: 2) wherein each of X_2 and X_6 is independently selected from the 20 genetically coded L-amino acids; X_3 is C; X_4 is R, H, L or W; X_5 is M, F or I; X_7 is D, E, I, L or V; and X_8 is C.

28. The method of claim 23 wherein said agonist comprises a sequence of amino acids $X_1YX_2X_3X_4X_5GPX_6TWX_7X_8X_9X_{10}X_{11}$ (SEQ ID NO: 3) wherein each of X_1 , X_2 , X_6 , X_9 , X_{10} , and X_{11} is independently selected from any one of the 20 genetically coded L-amino acids; X_3 is C; X_4 is R, H, L or W; X_5 is M, F or I; X_7 is D, E, I, L or V; and X_8 is C.

29. The method of claim 23 wherein said agonist comprises a sequence of amino acids $X_1YX_2X_3X_4X_5GPX_6TWX_7X_8X_9X_{10}X_{11}$ (SEQ ID NO: 3) wherein each of X_1 , X_2 , and X_{11} , is independently selected from any one of the 20 genetically coded L-amino acids; X_3 is C; X_4 is R or H; X_5 is F or M; X_6 is I, L, T, M or V; X_7 is D or V; X_9 is G, K, L, Q, R, S, or T; and X_{10} is A, G, P, R, or Y.

30. The method of claim 23 wherein said agonist comprises a sequence of amino acids $X_1YX_2X_3X_4X_5GPX_6TWX_7X_8X_9X_{10}X_{11}$ (SEQ ID NO: 3) wherein X_1 is D, E, L, N, S, T or V; X_2 is A, H, K, L, M, S, or T; X_3 is C; X_4 is R or H; X_5 is M, F or I; X_6 and X_{11} are independently any one of the 20 genetically coded L- amino acids; X_7 is D, E, I, L or V; X_8 is C; X_9 is K, R, S, or T; and X_{10} is P.

31. The method of claim 23 wherein said agonist is selected from a group consisting of:

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	GGLYLCRFGPVTWDCGYKGG	(SEQ ID NO:7);
	GGTYSCHFGPLTWVCKPQGG	(aka EMP-1) (SEQ ID NO:8);
	GGDYHCRMGPPLTWVCKPLGG	(SEQ ID NO:9);
	VGNYMCHFGPITWVCRPGGG	(SEQ ID NO:10);
5	GGVYACRMGPITWVCSPLGG	(SEQ ID NO:11);
	VGNYMAHMGPIWVCRPGG	(SEQ ID NO:12);
	GGTYSCHFGPLTWVCKPQ	(aka EMP-16) (SEQ ID NO:13);
	GGLYACHMGPMTWVCQPLRG	(aka EMP-36) (SEQ ID NO:14);
	TIAQYICYMGPETWECRPSKA	(aka EMP-38) (SEQ ID NO:15);
	YSCHFGPLTWVCK	(aka EMP-20) (SEQ ID NO:16);
	YCHFGPLTWVC	(aka EMP-23) (SEQ ID NO:17);
	SCHFGPLTWVCK	(aka EMP-24) (SEQ ID NO:18);
	GGTASCHFGPLTWVCKPQGG	(aka EMP-6) (SEQ ID NO:19);
	GGTYSCHFAPLTWVCKPQGG	(aka EMP-9) (SEQ ID NO:20);
	GGTYSCHFGPLTWVCKPQGG	(aka EMP-27) (SEQ ID NO:21);
	TYSCHFGPLTWVCKPQGG	(aka EMP-17) (SEQ ID NO:22);
	TYSCHFGPLTWVCKPQ	(aka EMP-18) (SEQ ID NO:23);
	YSCHFGPLTWVCKP	(aka EMP-19) (SEQ ID NO:24);
	YSCHFGPLTWVC	(aka EMP-21) (SEQ ID NO:25);
20	YSCHFGALTWVCK	(aka EMP-22) (SEQ ID NO:26);
	GGCRIGPITWVCGG	(aka EMP-25) (SEQ ID NO:27);
	HFGPLTWV	(aka EMP-26) (SEQ ID NO:28);
	GGTTSCHFGPLTWVCKPQGG	(aka EMP-7) (SEQ ID NO:29);
	GGTFSCHFGPLTWVCKPQGG	(aka EMP-8) (SEQ ID NO:30);
25	GGTYSCHFGALTWVCKPQGG	(aka EMP-10) (SEQ ID NO:31);
	GGTYSCHFGPATWVCKPQGG	(aka EMP-11) (SEQ ID NO:32);
	GGTYSCHFGPLAWVCKPQGG	(aka EMP-12) (SEQ ID NO:33);
	GGTYSCHFGPLTAVCKPQGG	(aka EMP-13) (SEQ ID NO:34);
	GGTYSCHFGPLTFVCKPQGG	(aka EMP-14) (SEQ ID NO:35);
30	GGTYSCHFGPLTWVCKAQGG	(aka EMP-15) (SEQ ID NO:36);

GGTXSCHFGPLTWVCKPQGG (aka EMP-28, X = D-Tyr) (SEQ ID NO:37);
GGTXSCHFGPLTWVCKPQGG (aka EMP-29, X = *p*-NO₂-Phe) (SEQ ID NO:38);
GGTXSCHFGPLTWVCKPQGG (aka EMP-30, X = *p*-NH₂-Phe) (SEQ ID NO:39);
GGTXSCHFGPLTWVCKPQGG (aka EMP-31, X = *p*-F-Phe) (SEQ ID NO:40);
5 GGTXSCHFGPLTWVCKPQGG (aka EMP-32, X = *p*-I-Phe) (SEQ ID NO:41);
GGTXSCHFGPLTWVCKPQGG (aka EMP-33, X = 3,5-dibromo-Tyr)
(SEQ ID NO:42);
Ac-GGTYSCHFGPLTWVCKPQGG (aka EMP-34) (SEQ ID NO:43);
GGLYACHMGPMTWVCQPLGG (aka EMP-35) (SEQ ID NO:44);
LGRKYSCHFGPLTWVCQPAKGD (aka EMP-37) (SEQ ID NO:45); and
GGTYSEHFGPLTWVKKPQGG (aka EMP-39) (SEQ ID NO:46).

32. The method of claim 23 wherein said peptide dimers are formed with a polyethylene glycol linker through a covalent bond.
33. A method of preparing a cell surface receptor agonist comprising dimerizing a cell surface antagonist.
34. The method of claim 33 wherein said cell surface antagonist receptor is a GH antagonist, PDGF antagonist, EGF antagonist, G-CSF antagonist, EGF antagonist, GM-CSF antagonist, TPO antagonist, VEGF antagonist, FGF antagonist, insulin antagonist, IL-3 antagonist, IL-5 antagonist, IL-6 antagonist, or an IL-2 antagonist.
35. The method of claim 33 wherein said cell surface receptor antagonist is an EPO-R antagonist.

36. The method of claim 35 wherein said antagonist comprises a sequence of amino acids $(X_1X_2)_nX_3X_4X_5GPX_6TWX_7X_8$ (SEQ ID NO: 19) wherein X_6 is selected from the 20 genetically coded L-amino acids; X_3 is C; X_4 is R, H, L or W; X_5 is M, F or I; X_7 is D, E, I, L or V; X_8 is C; X_2 is selected from the 20 genetically coded L-amino acids, n is 0 or 1 and X_1 is any of the 20 genetically coded L-amino acids except Y (tyrosine).

37. The method of Claim 33 where said antagonist is SCHFGPLTWVCK (SEQ ID NO: 18).

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